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REVIEW

A review on herbal antiasthmatics

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Abstract In traditional systems of medicine, many plants have been documented to be useful for the treatment of various respiratory disorders including asthma. In the last two decades the use of medicinal plants and natural products has been increased dramatically all over the world. Current synthetic drugs used in pharmacotherapy of asthma are unable to act at all the stages and targets of asthma. However some herbal alternatives employed in asthma are proven to provide symptomatic relief and assist in the inhibition of disease progression also. The herbs have shown interesting results in various target specific biological activities such as bronchodilation, mast cell stabilization, anti-anaphylactic, anti-inflammatory, anti-spasmodic, anti-allergic, immunomodulatory and inhibition of mediators such as leukotrienes, lipoxygenase, cyclooxygenase, platelet activating, phosphodiesterase and cytokine, in the treatment of asthma. This paper is an attempt to classify these pharmacological and clinical findings based on their possible mechanism of action reported. It also signifies the need for development of polyherbal formulations containing various herbs acting at particular sites of the pathophysiological cascade of asthma for prophylaxis as well as for the treatment of asthma.

Keywords Asthma · Current therapy · Herbal therapy · Poly herbal formulations · Ayurvedic drugs · Medicinal plants

Introduction

According to the National Institute of Health (NIH), asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, neutrophils and epithelial cells (NIH 1997). Asthma is caused by a very complex interaction between inflammatory cells and mediators. Herbal approaches have regained their popularity, for the treatment of asthma, with their efficacy and safety aspects being supported by controlled clinical studies (Huntley and Ernst 2000). Ongoing worldwide research has also provided valuable clues regarding the precise mechanism of action of these herbal alternatives (Goyal et al. 2007).

Pharmacotherapy of bronchial asthma

In the past most clinicians managed asthma mainly according to the patient's symptom. Asthma was regarded primarily as a problem of bronchospasm and measures to prevent or reverse bronchospasm comprised the mainstay of therapy. However, during early 1980s when asthma emerged as an inflammatory rather than primarily a bronchospastic disorder, the basic approach switched from control of symptoms to control of underlying airway inflammation (Barns 1989). According to guidelines of The National Asthma Education and Prevention Program's

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(NAEPP) guidelines for the diagnosis and management of asthma, the treatment should have following goals:

1. Maintain normal activity levels, including exercise.
2. Maintain normal or near normal pulmonary function.
3. Prevent chronic and troublesome symptoms.
4. Prevent recurrent exacerbations.
5. Avoid adverse effects from medications.

The pharmacological management of asthma depends upon frequency and severity of patient's symptoms. Infrequent attacks can be managed by treating each attack when it occurs, but with more frequent attacks preventive therapy needs to be used. The following categories of drugs are used in asthma:

1. Bronchodilators
   - 1.1 β-adrenergic agonists: e.g. Metaproterenol, terbutaline, albuterol, formoterol, bitolterol, salmeterol, pirbuterol.
   - 1.2 Anticholinergics: e.g. Ipratropium bromide, Tiotropium bromide.
   - 1.3 Methylxanthines: e.g. Theophylline, aminophylline, acepiphylline, diprophylline, proxophylline.
2. Anti-inflammatory agents
   - 2.1 Corticosteroids: e.g. Prednisolone, dexamethasone, beclomethasone dipropionate, dexamethasone, budesonide, fluticasone.
   - 2.2 Anti-leukotrienes: e.g. Probilukast, Iralukast, Zieluton, Montelukast, zafirlukast, pranlukast.
   - 2.3 Mast Cell Stabilizers: e.g. Cromolyn Sodium, Nedocromil sodium.

Bronchodilators

Bronchodilator drugs have an anti-bronchoconstrictor effect that may be demonstrated directly in vitro by drug-induced relaxation of precontracted airways (Barns et al. 1988). Bronchodilators promptly reverse airway obstruction in asthmatics. This action believed to be mediated by a direct effect on airway smooth muscle. However, additional pharmacologic effects on the other airway cells (such as capillary endothelium to reduce microvascular leakage and mast cells to reduce release of bronchoconstrictor mediators) may contribute to the overall reduction in airway narrowing. Only three types of bronchodilators are in current clinical use: β-adrenergic agonists, methylxanthines, and anticholinergics.

β-adrenergic agonists

Epinephrine has been used to treat asthma since the beginning of the 20th century. β Adrenergic agonists are most widely used and effective bronchodilators for the treatment of asthma. Bronchodilation is mediated by β_2 receptors; β_2 selective drugs (Salmeterol and Formoterol) have been developed that have long duration of effect. β Adrenergic agonists lead to relaxation of bronchial smooth muscle that promote bronchodilation. Activation of adenylate cyclase increases the concentration of intracellular cyclic adenosine 3′, 5′-monophosphaste (cAMP), leading to activation of specific cAMP-dependent protein kinases that cause relaxation. Relaxation may also be due to inhibition of myosin phosphorylation. β-adrenergic agonists reverse bronchoconsriction irrespective of the contractile agent. β-adrenergic agonists prevent release of mediators from a number of inflammatory cells in vitro (Church and Hiroi 1987). In addition, β adrenergic agonists increase mucus secretion from submucosal glands and ion transport across airway epithelium. These effects enhance mucociliary clearance caused by asthma (Pavia et al. 1980).

The inhaled route of administration is preferable to the oral route because adverse effects caused by systemic action of the drug are less and also because this route may be more effective. The inhaled drug reaches surface cells (e.g., mast cells or epithelial cells), which are less accessible to the orally administered drug.

Metaproterenol, terbutaline, albuternol, formopterol, bitolterol, salmeterol, and pirbuterol are the classic examples of selective β_2-adrenergic agonists.

β agonists improve respiratory symptoms and exercise tolerance despite the small improvement in spirometric measurements. The long acting β-agonists decrease infection exacerbations as an additional potential benefit. Salmeterol has been shown to reduce adherence of bacteria such as *H. influenza* to airway epithelial cells.

β_2 selective agents cause tachycardia and palpitation by reflex cardiac stimulation secondary to peripheral vasodilation. Muscle tremor is caused by stimulation of β_2 adrenergic receptors in skeletal muscle and is the primary adverse effect of albuterol and bitolterol. Transient hypokalemia may be induced by high dose of these agents.

Anticholinergics

Datura plants contain the muscarinic antagonist and were smoked for relief of asthma centuries ago. Now a days, atropine and ipratropium bromide are the most commonly available anticholinergics.

Antimuscarinic agents specifically antagonize muscarinic receptors. They inhibit reflex cholinergic bronchoconstriction and do not significantly block the direct effects of inflammatory mediators such as histamine and leukotrienes on bronchial smooth muscle and vessels. When given by inhalation, anticholinergics produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial

smooth muscle. This activity blocks acetylcholine with the net effect being a reduction in cyclic guanosine monophosphate (cGMP) that normally acts to constrict bronchial smooth muscle. Anticholinergic drugs usually are less effective as bronchodilators in asthmatic subjects than β adrenergic agonists. Nevertheless, they may have an additive effect with β adrenergic agonists.

Atropine reduces mucociliary clearance in normal subjects and in patients with asthma and chronic bronchitis, but the quaternary derivative, ipratropium bromide, even when given in high doses, has no such detectable effect either on normal subjects or in patients with airway disease (Pavia et al. 1980).

Ipratropium bromide has been shown to decrease the effectiveness of voluntary cough on clearing mucus from the airways, which may affect its role in the treatment of patients who have excessive mucus production. Ipratropium has a slower onset of action and a more prolonged bronchodilator effect compared with standard β_2-agonists and has been considered to be less suitable for use on an as needed basis for immediate relief of bronchospasm.

The lack of systemic absorption of ipratropium greatly diminishes the anticholinergic side effects such as blurred vision, urinary retention, nausea, and tachycardia associated with atropine. A significant unwanted effect of inhaled ipratropium bromide is dryness of mouth and throat, bitter taste, cough and nausea. Nebulized ipratropium bromide may precipitate glaucoma in elderly patients because of its direct mydriatic effect on the eye. During sleep, ipratropium also has been shown to improve arterial oxygen saturation and sleep quality.

Tiotropium bromide is a long acting quaternary anticholinergic agent. Tiotropium in human lungs shows approximately 10 fold more potency than ipratropium and protects against cholinergic bronchoconstriction for greater than 24 h.

Methylxanthines

Methylxanthines such as theophylline are related to caffeine and have been used to treat asthma since 1930. The methylxanthines may produce bronchodilation through numerous mechanisms, including,

- inhibition of phosphodiesterase, thereby increasing cAMP levels
- inhibition of calcium ion influx into smooth muscle
- prostaglandin antagonism
- stimulation of endogenous catecholamines
- adenosine receptor antagonism
- Inhibition of release of mediators from mast cells and leukocytes.

Theophylline inhibits release of mediators from mast cells, increases mucocilliary clearance, and prevents the development of micro vascular leakiness, as would an "anti-inflammatory" drug (Persson and Draco 1988). Theophylline also inhibits some functions of T lymphocytes, which may be relevant to control of chronic inflammation of the airway.

For nocturnal asthma, a single dose of slow release theophylline at bedtime often is effective. This has been demonstrated to reduce overnight declines in FEV_1 and morning respiratory symptoms. Taken alone it increases exercise tolerance without improving spirometry tests.

Other theophylline salts, such as choline theophyllinate, offer no advantages over theophylline. The ethylenediamine component of aminophylline has been implicated in allergic reactions. Some derivates such as acepiphylline, diprophylline, and proxophylline, are less effective than theophylline (Weinberger 1984). The most common adverse effects are headache, nausea and vomiting, abdominal discomfort, and restlessness.

Anti-inflammatory drugs

Although the type of inflammatory responses may differ among diseases, inflammation is a common denominator of several lung diseases. Anti-inflammatory drugs suppress the inflammatory response by inhibiting infiltration and activation of inflammatory cells as well as their synthesis or release of mediators or effects of inflammatory mediators themselves.

Corticosteroids

Since asthma is viewed as a chronic inflammatory disease and inhaled corticosteroids are known to have low toxicity, they may be considered as first line therapy (Barns 1989). Prednisolone and dexamethasone were effective when they were given systematically to treat asthma but they had no anti-asthmatic activity when they were given by inhalation. Other corticosteroids e.g. beclomethasone dipropionate (BDP), betamethasone and budesonide, were effective in treating asthma when given by inhalation. The antiasthmatic potency of an inhaled steroid is approximately proportional to its potency as an anti-inflammatory agent.

Corticosteroids inhibit the release of arachidonic acid metabolites and platelet activating factor (PAF) from lungs and macrophages by enhancing the production of proteins called lipocortin. Thereby they inhibit the formation of prostaglandins and leukotrienes. These effects occur because of ability of steroid—receptor complex to be transported to the nucleus, where it initiates DNA transcription of specific mRNAs. Corticosteroids potentially inhibit the accumulation of neutrophils, inhibit secretion of human pulmonary macrophages of leukotrienes and prostaglan-

dins, inhibit formation of interleukins (ILs) such as IL-1, IL-2, IL-3 and IL-5, inhibit degranulation and adherence of eosinophils, reduce number of circulating T lymphocytes and formation of an IgE binding suppressive factor. Steroids prevent and reverse the increase in vascular permeability due to inflammatory mediators and may therefore lead to resolution of airway edema. Corticosteroids remain the most effective therapy available for asthma but the legitimate fear of their adverse effects makes using them difficult. Steroids potentiate the effects of β adrenergic agonists on bronchial smooth muscle (Barns 1989). Methylprednisolone is given intravenously to patients with severe acute asthma. Inhaled steroids have no proven value in the management of acute asthma. Patients with chronic bronchitis occasionally respond to steroids, possibly because some have an element of undiagnosed asthma.

Corticosteroids inhibit release of ACTH and secretion of cortisol by a negative feed back effect on the pituitary gland. Adverse effects of corticosteroids include fluid retention, increased cell mass, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataract, and psychosis (Dajani et al. 1981).

Anti-leukotrienes

Leukotrienes possess potent pro-inflammatory actions resulting in increased vascular permeability, mucus secretion and bronchial hyperresponsiveness. They are derived from the 5-lipoxygenase pathways in mast cells, eosinophils and macrophages. Anti-leukotrienes improve lung function and diminish symptoms, exacerbation rate and the need for rescue bronchodilator. These are drugs of choice in case of aspirin induced asthma, in which patients have high LTE_4 levels in urine and nasal secretions and even higher after taking aspirin (Christie et al. 1992).

Leukotriene modifiers are drugs that modify the response of these mediators of inflammation by one of the four ways (Drazen 1997).

a) Cysteinyl LT receptor inhibitors
   C-LTs promote eosinophil influx, bronchospasm and mucus hypersecretion, all are considered hallmarks of asthma. C-LT receptor inhibitors antagonize or inhibit leukotrienes predominantly LTD_4. These agents inhibit phospholipases, prostaglandins, leukotrienes, and IL-1 synthesis. Probilukast and Iralukast belong to this class (Drazen 1997; Floreani and Rennard 1999).
b) 5-lipoxygenase inhibitors
   They prevent the formation of leukotrienes by blocking a 5-lipoxygenase pathway in their synthesis. Zileuton, ZD-2138, ABt-761 belongs to this class (Floreani and Rennard 1999).
c) 5-lipoxygenase activating protein (FLAP) inhibitors
   MK-0591 and MK-886 attenuated the early and late asthmatic response following antigen challenge but not the attendant increase in airway responsiveness to spasmogens (Diamant et al. 1995).
d) Leukotrienes receptor antagonists

Montelukast, Zafirlukast, Pranlukast are selective and high affinity LT_1 antagonists (Adcock and Matthews 1998).

Zileuton has shown efficacy in exercise-induced asthma, aspirin induced bronchospasm and following chronic administration, an improvement in pulmonary function (FEV1) and a reduction in oral and inhaled corticosteroid use (Tamaoki et al. 1997). Furthermore, in a small study, zileuton attenuated both airway and blood eosinophilia in nocturnal asthmatics (Wenzel et al. 1995).

Zafirlukast has been demonstrated to attenuate the acute airway obstructive response to allergen and exercise challenge and to improve chronic asthma control both objectively (FEV1, nocturnal awakenings, β-agonist use) and subjectively.

Montelukast has been shown to block the early and late response to allergen challenge following single dosing, to improve FEV1 in both children (6–14 years) and adults and to protect against the development of exercise induced bronchoconstriction in both children and adults. Tolerance to the bronchoprotective effects of montelukast in attenuating exercise-induced bronchospasm does not develop following at least 12 weeks of therapy.

Pranlukast increases FEV1 within 1 h of dosing, improves patient summary symptom and nighttime asthma scores and reduces the use of rescue bronchodilators. In patients with moderate persistent asthma, it prevents exacerbations of asthma during reduction of high dose inhaled corticosteroids therapy (Tamaoki et al. 1997).

Mediator release inhibitors

Cromolyn sodium

Cromolyn Sodium (Sodium cromoglycate) is a derivative of khellin, an Egyptian herbal remedy. Cromolyn inhibited the release of mediators by allergen in passively sensitized animal and human lung preparations (Cox 1967). Cromolyn was classified as mast cell stabilizer. Cromolyn has variable inhibitory actions on other inflammatory cells including macrophages and eosinophils that may participate in allergic inflammation. In vivo cromolyn can block both the early response that may be mediated by mast cells to allergens and the late response and bronchial hyper responsiveness (Cockcroft and Murdock 1987). Cromolyn Sodium is used for prophylactic treatment and consequently needs to be taken regularly. It is the first choice anti-

inflammatory drug for children because it has few adverse effects (Bernstein 1985). Cromolyn sodium is classified as an antiallergic drug because it appears to have a specific effect on allergy based inflammation. Several other drugs also may be included in this category.

Nedocromil sodium is a new drug used for prophylaxis. It has a similar pharmacologic profile of activity to cromolyn, is more potent in various tests, and may have a longer duration of action. Ketotifen also is described as a drug to be used for prophylaxis against asthma.

Newer targets in asthma therapy

The current pharmacotherapeutic approaches to asthma have several limitations. First, there is no known asthma cure and little evidence that prevention is possible in susceptible persons. Hence, patients continue to be at risk of symptoms and exacerbations. Mortality remains a severe problem. Finally, the medications have adverse effects. There is even some evidence, albeit conflicting, that cataract formation, osteoporosis and growth impairment, as associated with systemic glucocorticoids, may arise from topical steroids, depending on dosages used. New inhalation devices and new generation beta-agonists are available. At the same time, new understanding of the molecular pathology of asthma has identified several novel therapeutic targets. Agents being tested in early phase clinical trials include antagonists of IgE, cytokines, adhesion molecules and transcription factors.

TXA_2 inhibitors

TXA_2 is a potent bronchoconstrictor, mucus producer and blood vessel permeability inducer and causes airway hyper responsiveness. Serabenast, domitroban and ozagrel are the

Table 1 Bronchodilators

Sr. No	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Adhatoda vasica* Nees	Leaves, Roots	Alkaloids	Paliwa et al. 2000
2.	*Albizzia lebbeck (Sareesha_ rakat)*	Stem bark/Aqueous	Saponins	Tripathi and Das 1977
3.	*Alstonia scholaris*	Leaves/Ethanol	Ditamine, Echitamine and Echitenines	Channa et al. 2003
4.	*Artemisia caerulescens*	Aerial parts/Butanol	Quercetin, isorhamnetin	Moran et al. 1989
5.	*Belamcanda chinensis*	Leaves/Ethanol	Tectorigenin	Singh and Agrawal 1990
6.	*Benincasa hispida*	Fruits/Methanol	Triterpenes,Glycosides, Sterols	Kumar and Ramu 2002
7.	*Cissampelos sympodialis*	Leaves and root bark/Aqueous	Warifteine, α-bisbenzylisoquinoline alkaloid	Thomas et al. 1995, 1997; Cortes et al. 1995
8.	*Clerodendron serratum*	Stem bark/Aqueous	Phenolic glycoside	Gupta 1968; Gupta and Tripathi 1973
9.	*Coleus forskohlii*	Roots	Forskolin (Diterpenoid)	Marone et al. 1987
10.	*Elaeocarpus spharicus*	Fruits/Aqueous, Pet-ether, Benzene, Acetone and ethanol	Glycoside, Steroids, Alkaloid, Flavanoids	Singh et al. 2000
11.	*Galphimia glauca*	Aerial/Alcohol extract/Ethyl-acetate	Tetragalloylquinic acid, Quercetin	Campos et al. 2001
12.	*Gardenia latifolia*	Bark	Saponins	Gupta 1974
13.	*Ginko biloba*	Leaves	Ginkgolides	Puglisi et al. 1988
14.	*Mikania glomerata*	Leaves/Aqueous, hydroalcohol	Coumarin	Soares de Moura et al. 2002
15.	*Lepidium sativum*	Seeds/Ethanol fractions	Alkaloids, Flavonoids	Mali et al. 2008
16.	*Ocimum sanctum*	Leaves/Ethanol	Myrcenol, Nerol, Eugenol	Singh and Agrawal 1991
17.	*Passiflora incarnata*	Leaves/Methanol	Alkaloids	Dhawan et al. 2003
18.	*Pavetta crassipes*	Leaves/Aqueous	Flavanoids, tannins, anthraquinones	Amos et al. 1998
19.	*Picrorrhiza kurroa*	Roots/	Androsin	Stuppner et al. 1991
20.	*Sarcostemma brevistigma*	Twigs/Alkaloidal fraction	Bregenin	Saraf and Patwardhan 1988b
21.	*Tephrosia purpurea*	Aerial parts/Ethanol extract	Flavanoids, Tephrosin	Gokhale et al. 2000
22.	*Tylophora indica*	Leaves/Alkaloidal fraction	Tylophorine	Nayampalli et al. 1986
23.	*Vitex negundo*	Leaves/Ethanol	Casticin, isoorientin Chrysophenol D, Luteolin	Nair and Saraf 1995
24.	*Rosmarinus officinalis*	Shrub/Aqueous	Caffeic acid (CA) and Rosmarinic acid	Aqel 1991
25.	*Ephedra sinica*	Stems	Ephedrine	Akiba et al. 1979
26.	*Gleditsia sinensis Lam.*	Leaves/Decoctions		Dai et al. 2002

examples of these TXA_2 synthetase inhibitors. Ozagrel reduced cough sensitivity to capsaicin and bronchoconstriction due to acetaldehyde. TXA_2 antagonists *BAY u3405* produced a modest decrease in airways responsiveness to methacholine following 2 weeks treatment in asthmatics.

Tachykinin receptor antagonists

The first nonpeptide tachykinin receptor antagonist was *CP-96345*, which is a potent NK_1 receptor antagonist. *SR 48968*, *GR 159897* and *SR 144190* are selective nonpeptide NK_2 receptor antagonists. *SR 142801* and *SB 223412* are selective NK-3 receptor antagonists.

Tryptase inhibitors

Tryptase inhibitors inhibit both early and late reactions. *APC-366* inhibited antigen induced late phase response and bronchial hyperresponsiveness to carbachol in sheep. Lactoferrin disrupts the quaternary structure

Table 2 Mast cell stabilizers

Sr.No.	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Achyranthes aspera*	Aerial parts/Aqeous	Oleanolic acid	Agrawal and Mehta 2005
2.	*Albizzia lebbeck*	Stem bark/Aqueous	Saponins	Tripathi et al. 1979
3.	*Allium cepa*	Bulbs/Juice	α and β unsaturated Thiosulphinates	Johri et al. 1985
4.	*Aquillaria agallocha*	Stem/Aqueous extract	Triterpenoids	Kim et al. 1997
5.	*Azadirachta indica*	Leaves/Juice	Nimbin, nimbinine, Nimbandiol, quercetin	Acharya et al. 2003
6.	*Bacopa monniera*	Leaves/Ethanol	Bacosides, Alkaloids,Glycosides	Samiulla et al. 2001
7.	*Bidens parviflora*	Aerial parts	Glycosides	Wang et al. 2001
8.	*Calotropis procera*	Latex	α-amyrin,β-amyrin calotropin (Triterpenoid)	Kumar and Basu 1994
9.	*Cassia alata*	Leaves/Ethanol	Anthraquinones, Flavanoids	Palanichamy et al. 1991
10.	*Cassia obtusifolia*	Seeds/Glycosidal fraction	Anthraquinones, Betulinic acid	Kitanaka et al. 1998
11.	*Cassia torosa*	Seeds	Gentiobiosides	Kanno et al. 1999
12.	*Cedrus deodara*	Wood oil	Himacholol	Shinde et al. 1999
13.	*Citrus unshiu*	Peels/	Flavanoids	Kim et al. 1999
14.	*Clerodendron serratum*	Bark/Aqueous	Phenolic glycoside	Gupta 1968
15.	*Cnidium monnieri*	Fruits/Ethanol	Osthol	Chen et al. 1988
16.	*Coleus forskohlii*	Roots	Forskolin (diterpenoid)	Marone et al. 1987
17.	*Crinum glaucum*	Leaves/Aqueous	Alkaloids, lycorine, crinamine	Okpo and Adeyemi 2002
18.	*Curcuma longa*	Rhizome	Tumerones, curcuminoids	Ammon and Wahl 1991
19.	*Drymaria cordata*	Methanol extracts		Mukherjee et al. 1997
20.	*Elaeocarpus spharicus*	Fruits/Aqueous, Pet-ether, Benzene, Acetone and ethanol	Glycoside, Steroids, Alkaloid, Flavanoids	Singh et al. 2000
21.	*Gleditsia sinensis*	Fruits/Ethanol	Saponins	Dai et al. 2002
22.	*Impatiens textori*	Flowers/Ethanolic	Apigenin, uteolin, chrysoeriol	Ishiguro et al. 2000
23.	*Inula racemosa*	Roots/Alcohol	Inulolide-a new Sesquiterpene lactone	Srivastava et al. 1999
24.	*Magnolia officinalis*	Bark/Aqueous	Honokiol, Magnolol	Shin et al. 2001b
25.	*Mentha piperita*	Leaves	Flavanoidal glycosides	Inoue et al. 2002
26.	*Ocimum sanctum*	Leaves/Aqueous	Myrcenol, Nerol, Eugenol	Sen 1993
27.	*Picrorrhiza kurroa*	Roots/	Androsin	Stuppner et al. 1991
28.	*Solanum xanthocarpum*	Roots/Alkaloidal fraction	Solasodine	Chitravanshi et al. 1990
29.	*Striga orobanchioids*	Aerial parts/Ethanol		Harish et al. 2001
30.	*Tephrosia purpurea*	Aerial parts/Ethanol extract	Flavanoids, Tephrosin	Gokhale et al. 2000
31.	*Terminalia chebula*	Fruits/Aqueous	Ellagic acid, Tannins Chebulagic acid	Shin et al. 2001a
32.	*Tinospora cordifolia*	Stem/Aqueous	Tinosporin	Nayampalli et al. 1986
33.	*Tylophora asthmatica*	Leaves/Alkaloidal	Tylophorine	Geetha et al. 1981
34.	*Vitex negundo*	Leaves/Ethanol	Casticin, isoorientin Chrysophenol D, Luteolin	Nair et al. 1994

of tryptase, also attenuates antigen induced late response and bronchial hyperresponsiveness in allergic sheep.

Cytokine inhibitors

One of the novel approaches for the treatment of asthma is to target cytokines and develop cytokine modulators as drugs. Two humanized anti-IL-5 monoclonal antibodies, *Sch-55700* and *SB-240563* reduced blood eosinophil count for several weeks and prevented eosinophils recruitment into the airways after allergen challenge in asthmatic patients. IL-5 signaling inhibitor *GCC-AP0341* inhibited IL-5 mediated survival of eosinophils. IL-4 receptor antibodies inhibited allergen induced airway hyperresponsiveness, goblet cell metaplasia and pulmonary eosinophilia in a murine model.

Chemokine inhibitors

A variety of chemokines, one of which is the chemoattractant eotaxin, are secreted by inflamed lung tissue thereby attracting eosinophils. Eotaxin receptor blockers are being investigated, as eosinophils are believed to be major contributors to the pulmonary damage seen in asthma. Monoclonal antibody (7B11) for human CCR_3 has shown to completely block the binding and signaling of the known CCR_3 ligands, thus blocking the chemotactic response of human eosinophils to all chemokines.

Adhesion molecule antagonists

Interactions of eosinophils with intra cellular adhesion molecule-1 (ICAM-1) are thought to be necessary for eosinophils recruitment into airways. Antibodies to ICAM-1

Table 3 Anti-allergics

Sr. No.	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Adhatoda vasica*	Leaves/Methanol	Vasicinol, vasicine	Muller et al. 1993; Kumar Suresh 1979
2.	*Albizzia lebbeck*	Stem bark/Aqueous	Saponins	Baruah et al. 1997; Suresh et al. 1981
3.	*Alisma orientale*	Rhizomes/Aqueous, Methanol	Alisol B monoacetate, Alismaketones-B 23-acetate and –C 23-acetate	Kubo et al. 1997
4.	*Aquillaria agallocha*	Stem/Aqueous extract	Triterpenoids	Kim et al. 1997
5.	*Asiasarum sieboldi*	Roots/Methanol	Methyleugenol, gamma-asarone, Elemicin, Asarinin	Hashimoto et al. 1994
6.	*Camellia sinensis*	Leaves	Flavanoids	Suzuki et al. 2000
7.	*Centipeda minima*	Aerial parts	Flavanoids, Pseuodoguainolide, sesquiterpene lactones	Wu et al. 1985
8.	*Citrus unshiu*	Peels/	Flavanoids	Kim et al. 1999
9.	*Cnidium monnieri*	Fruits/Ethanol	Osthol	Matsuda et al. 2002
10.	*Crinum glaucum*	Leaves/Aqueous	Alkaloids, lycorine, crinamine	Okpo and Adeyemi 2002
11.	*Curcuma longa*	Rhizomes	Curcumin and tetrahydrocurcumin	Suzuki et al. 2000
12.	*Dalbergia odorifera*	Heart Wood	Flavanoids, Tannins	Chan et al. 1998
13.	*Desmodium adscendins*	Aqueous	Triterpenoid Saponin	Addy 1989
14.	*Galphimia glauca*	Aerial/Alcohol extract/ Ethyl-acetate	Tetragalloylquinic acid, Quercetin	Neszmelyi et al. 1993
15.	*Ginko biloba*	Leaves	Ginkgolides	Touvay et al. 1985
16.	*Gleditsia sinensis*	Fruits/Ethanol	Saponins	Dai et al. 2002
17.	*Hydrangea macrophylla*	Leaves	Glycosides	Matsuda et al. 1999
18.	*Inula racemosa*	Roots/Alcohol	Inulolide-a new Sesquiterpene lactone	Srivastava et al. 1999
19.	*Magnolia officinalis*	Bark/Aqueous	Honokiol, Magnolol	Shin et al. 2001b
20.	*Sarcostemma brevistigma*	Twigs/Alkaloidal fraction	Bregenin	Saraf and Patwardhan 1988a
21.	*Solanum xanthocarpum*	Roots/Alkaloidal fraction	Solasodine	Chitravanshi et al. 1990
22.	*Terminalia chebula*	Fruits/Aqueous	Ellagic acid, Tannins Chebulagic acid	Shin et al. 2001a
23.	*Vitex negundo*	Leaves/Ethanol	Casticin, isoorientin Chrysophenol D, Luteolin	Nair and Saraf 1995

Table 4 Anti-inflammatory agents

Sr.No.	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Asystasia gangetica*	Leaves/Methanol, Ethyl Acetate	Isoflavone glycoside, dalhorinin	Akah et al. 2003
2.	*Aloe vera Tourn.ex Linn. (Liliaceae)*	Leaves/Aqueous, Chloroform and ethanol	Anthraquinones, sterols, saponins and carbohydrate	Vazquez et al. 1996
3.	*Bryonia laciniosa*	Leaves/chloroform extract	Flavonoids	Gupta et al. 2003
4.	*Calotropis procera*	Latex	α-amyrin,β-amyrin calotropin (Triterpenoid)	Kumar and Basu 1994
5.	*Cinnamonun Zeylanicum*	oil	Eugenol, cinnamic aldehyde and α-terpeniol.	
6.	*Curcuma longa*	Rhizomes	Tumerones, curcuminoids	Ammon and Wahl 1991
7.	*Dalbergia odorifera*	Heart Wood	Flavanoids, Tannins	Chan et al. 1998
8.	*Elaeocarpus spharicus*	Fruits/Aqueous, Pet-ether, Benzene, Acetone and ethanol	Glycoside, Steroids, Alkaloid, Flavanoids	Singh et al. 2000
10.	*Nelsonia canescens*	Leaf/ethanol extract	Flavonoids	Owoyele et al. 2005
11.	*Indigofera tinctoria*	Whole plant/methanol	Polyphenols	Oli et al. 2005
12.	*Butea frondosa* Koen.	Leaves/Aqueous	Flavonoid, glycosides, proteins and amino acids.	Mengi and Deshpande 1999
13.	*Ocimum sanctum*	Leaves/Aqueous	Myrcenol, Nerol, Eugenol	Singh and Agrawal 1991
14.	*Ophiopogon japonicus*	Root/aquoes extract	Ruscogenin and ophiopogonin D	Kou et al. 2005
15.	*Pavetta crassipes*	Leaves/Aqueous	Flavanoids, tannins, anthraquinones	Amos et al. 1998
16.	*Tylophora asthmatica*	Leaves/Alkaloidal	Tylophorine	Manez et al. 1990

Table 5 Anti-spasmodic agents

Sr. No.	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Aegle marmelos*	Leaves/Ethanol	Aegelin, Aegelemine,Aegeline	Arul et al. 2004
2.	*Asiasarum sieboldi*	Roots/Methanol	Methyleugenol, gamma-asarone, Elemicin, Asarinin	Hashimoto et al. 1994
3.	*Asystasia gangetica*	Leaves/Methanol, Ethyl acetate	Isoflavone glycoside, dalhorinin	Akah et al. 2003
4.	*Bacopa monniera*	Leaves/Ethanolic	Bacosides, Alkaloids,Glycosides	Dar and Channa 1997; Channa et al. 2003
5.	*Belamcanda chinensis*	Leaves/Ethanol	Tectorigenin	Singh and Agrawal 1990
6.	*Cissampelos glaberrina*	Leaves, Root Bark/Aqueous	Warifteine, α-bisbenzylisoquinoline alkaloid	Thomas et al. 1995; Cortes et al. 1995
7.	*Clerodendron serratum*	Stem bark/Aqueous	Phenolic glycoside	Gupta 1968
8.	*Cnidium monnieri*	Fruits/Ethanol	Osthol	Chen et al. 1988
9.	*Coleus forskohlii*	Roots	Forskolin (diterpenoid)	Marone et al. 1987
10.	*Crinum glaucum*	Leaves/Aqueous	Alkaloids, lycorine, crinamine	Okpo and Adeyemi 2002
11.	*Drymis winteri*	Bark	Terpene	Sayah et al. 1998
12.	*Ferula ovina*	Aerial parts/Ethanol	Carvacrol, alpha-pinene, geranyl isovalerate and geranyl propionate	Khalil et al. 1990
13.	*Ferula sinica*	Roots/Ethanol	Resins	Aqel et al. 1991
14.	*Pavetta crassipes*	Leaves/Aqueous	Flavanoids, tannins, anthraquinones	Amos et al. 1998
15.	*Saussurea leppa*	Alkaloidal fraction	Sesquiterpene lactone, Terpenoids	Dutta et al. 1968
16.	*Striga orobanchioids*	Aerial parts/Ethanol	??	Harish et al. 2001
17.	*Thymus vulgaris*	Ethanol	Flavanones	Meister et al. 1999
18.	*Tylophora asthmatica*	Leaves/Alkaloidal	Tylophorine	Haranath and Shyamalakumari 1975; Udapa et al. 1991

blocked both eosinophils recruitment into the airways in the monkey model of asthma and importantly the increase in airway reactivity associated with allergen challenge

Phosphodiesterase inhibitors

Considerable interest has been generated in the potential utility of isoenzyme-selective inhibitors of cyclic nucleotide Phosphodiesterase (PDE) in the treatment of asthma and other inflammatory disorders. The scientific foundation for this interest is based upon two fundamental principles. First, inhibition of PDE activity increases the cellular content of two key second messengers, cAMP and cGMP, thereby activating specific protein phosphorylation cascades that elicit a variety of functional responses. Increases in cAMP content suppress a broad array of functions in inflammatory and immune cells. Both cAMP and cGMP mediate bronchodilation. PDE3 inhibitor enoxamine was shown to decrease lung resistance and increase compliance in patients with decompensated chronic pulmonary disease. Benzafentrine administered to normal volunteers by inhalation produced bronchodilation. Zaprinast is PDE5 inhibitor; it reduced exercise-induced bronchoconstriction but not histamine-induced bronchoconstriction. Most of the work now is focused on selectively targeting PDE4, primarily because inhibitors of this isoenzyme family have a notably appealing therapeutic profile; broad-spectrum anti-inflammatory activity coupled with additional bronchodilatory and neuromodulatory action. Rolipram, *LAS-31025*, *RP-73401* and denbufylline are selective PDE_4 inhibitors. *SB 207499*, *V11294A*, *CP-220* and roflumilast are PDE_4 inhibitors with less gastrointestinal side effects.

Endothelin modulators

There are two approaches for ET-1 directed therapeutics- (1) Inhibitors of endothelin-converting enzyme (ECE), which mediates the synthesis of ET-1 from its precursor; (2) Receptor antagonists of the effects of ET-1 at the end organ level. These agents reverse and/or prevent the increase in pulmonary artery pressure and vascular remodeling elicited by acute or chronic hypoxia. Examples are BQ-123, SB-217242 and bosentan.

Herbal drugs in bronchial asthma

Many Ayurvedic plants have been described to be useful in the treatment of various bronchial disorders including

Table 6 Miscellaneous agents

Sr No	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
	Lipoxygenase inhibitors			
1.	*Allium cepa*	Bulbs/Juice	α and β unsaturated Thiosulphinates	Bayer et al. 1989
2.	*Boswellia serrata*	Gum resin/Ethanol	Bosewellic acid	Ammon et al. 1991
3.	*Coleus forskohlii*	Roots	Forskolin (diterpenoid)	Marone et al. 1987
4.	*Proustia pyrifolia*	Whole plant/methanol	B-sitosterol, quercetin and dihydroquercetin	Delporte et al. 2005
	Platelet Activating Factor (PAF) inhibitors			
1.	*Allium cepa*	Bulbs/Juice	α and β unsaturated Thiosulphinates	Dorsch et al. 1987
2.	*Galphimia glauca*	Aerial/Alcohol extract/ Ethyl-acetate	Tetragalloylquinic acid, Quercetin	Neszmelyi et al. 1993
3.	*Impatiens textori*	Flowers/Ethanol	Apigenin, uteolin, chrysoeriol	Ueda et al. 2003
4.	*Picrorrhiza kurroa*	Roots/	Androsin	Stuppner et al. 1991
	Cyclooxygenase inhibitor			
1.	*Allium cepa*	Bulbs/Juice	α and β unsaturated Thiosulphinates	Bayer et al. 1989
2.	*Magnolia obovate*	Stem bark	Magnolol and honokiol	Lee et al. 2005
3.	*Crataegus pionatifida*	Fruit	Flavanoids	Kao et al. 2005
	Interleukins (Ils) biosynthesis inhibitors			
1.	*Calocedrus formosana*	Bark/alcohol	Sugiol	Chao et al. 2005
2.	*Nidularium procerum*	Leaves/Aqeous extract		Vieira-de-Abreu et al. 2005
3.	*Walthenia indica*	Whole plant/	flavanoids	Rao et al. 2005
4.	*Mahonia aquifolium* Nutt. Berberidaceae	Stem bark/hydroalcohol extract	Polysaccharides Protoberberine and bisbenzylisoquinoline (BBI) alkaloids berbamine, tetrandrine	Kostalova et al. 2001
	Leukotriene biosynthesis inhibitors			
1.	*Nigella sativa*	Seeds oil	Thymoquinone (TQ)	El Gazzar et al. 2006

Table 7 Antianaphylactic drugs

Sr. No.	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Xanthii fructus*	Whole plant/Aquous	Saponin, flavones, Caffeic acid, 1,4-dicaffeoylquinic acid, sesquiterpene lactones	Hong et al. 2003
2.	*Lycopus lucidus*	Whole plant/Aqueous	Betulinic acid, pentacyclic Triterpenes	Shin et al. 2005
3.	*Poncirus trifoliata*	Fruit/Aqueous	Flavonoids	Kim et al. 1999
4.	*Trichopus zeylanicus*	Leaves/butanol	Lipoprotein/Glycolipoprotein	Subramoniam et al. 1999
5.	*Cryptotympana atrata*	Whole plant/Aquous	oleanolic acid	Shin et al. 1999
6.	*Striga orobanchioides*	Whole plant/Aquous, ethanolic	Flavonoids, apigenin and luteolin	Harish et al. 2001
7.	*Crinum glaucum*	Bulbs/Aqueous	Alkaloids	Okpo and Adeyemi 2002
8.	*Acanthopanax senticosus*	Stem/Aqueous	Acanthoside A, B & C, Chiisanoside, Senticoside, Saponin, flavones,	Yi et al. 2002
9.	*Syzygium aromaticum*	Flower bud/Aqueous	Phenols	Kim et al. 1998
10	*Terminalia chebula*	Fruit/Aqueous	Tannins	Shin et al. 2001a
11	*Vitex rotundifolia*	Fruit/Aqueous	Flavonoids	Shin et al. 2000

bronchial asthma (Kumar Suresh 1979). The use of medicinal plants and natural products increased dramatically in the last two decades in all over the world. More than 400 medicinal plant species have been used ethanopharmacologically and traditionally to treat the symptoms of asthmatic and allergic disorders worldwide.

Classification of anti asthmatic herbs based on mechanism of action

Some herbal alternatives employed in asthma are proven to provide symptomatic relief and assist in the inhibition of disease development as well. These herbs therefore have multifaceted roles to play in the management of asthma suggesting different sites of action within the body. Based on the possible mechanism of action reported, plant anti-asthmatics may be classified as shown in tables (Tables 1, 2, 3, 4, 5, 6, 7 and 8).

Conclusion

Herbal approaches have regained their popularity, with their efficacy and safety aspects being supported by controlled clinical studies. The herbal approaches have offered effective mast cell stabilizers like sodium cromolyn and sodium cromoglycate developed from khellin and anti-leukotriene products like—boswellic acids. Ongoing re-

Table 8 Immunomodulatory drugs

Sr. No.	Name of plant	Part used/extract/fraction	Major chemical constituent(s)	Reference
1.	*Picrorhiza scrophulariiflora*	Rhizomes/Pet. ether, Diethyl ether and methanol	Apocynin, androsin and picroside II	Smit et al. 2000
2.	*Trichilia glabra*	Leaf/Aqueous	Polysaccharides	Benancia et al. 2000
3.	*Cedrela tubiflora*	Leaf/Aqueous	Gallic acid, polysaccharides	Benancia et al. 1995
4.	*Ipomoea carnea*	Leaf/Aqueous	Nortropane alkaloids, calystegines β_2	Hueza et al. 2003
5.	*Withania somnifera*	Coded extracts		Rasool and Varalakshmi 2006
6.	*Clausena excauata*	Wood/Aqueous	Phenolic compounds, furanocoumarins, flavanoids and carbazole alkaloid	Manosroi et al. 2005
7.	*Magnifera indica*	Bark/Alcohol, ether	Magniferin	Makare et al. 2001
8.	*Cleome viscosa*	Aerial parts/Aqueous, ethanolic	Alkaloids, saponins	Tiwari et al. 2003
9.	*Plantago ovata*	Seeds/Aqueous	Polysaccharides glycosides	Rezaeipoor et al. 2000
10.	*Typhae angustifolia*	Pollen/ethanol	Phenolic compounds, flavonesTriterpenes And β-sitosterol	Qin and Sun 2005
11.	*Angelica sinensis*	Roots/Aqueous and ethanolic	Polysaccharides	Yang et al. 2006
12.	*Boerhaavia diffusa*	Roots/ethanol	Alkaloids	Mungantiwar et al. 1999
13.	*Tephrosia purpurea*	Aerial parts/Ethanol	Flavanoids	Damre et al. 2003

search worldwide has provided valuable clues regarding the precise mechanism of action of these herbal alternatives and these herbs, have shown interesting results in various target specific biological activities such as bronchodilation, mast cell stabilization, anti-anaphylactic, anti-inflammatory, anti-spasmodic, anti-allergic, immunomodulatory and inhibition of mediators *viz.,* leukotrienes, lipoxygenase, cyclooxygenase, platelet activating, phosphodiesterase and cytokine, in the treatment of asthma.

Some herbal alternatives employed in these traditions are proven to provide symptomatic relief and assist in the inhibition of disease development as well. In nutshell, attempt should be made to develop polyherbal formulations which contain various herbs acting at particular sites of the pathophysiological cascade of asthma for prophylaxis as well as for the treatment of asthma and subsequent clinical studies on them.

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